Applicant has annexed hereto marked-up versions of the amended abstract, specification paragraph and claims as **Exhibits B-D**, respectively.

In view of the arguments below, applicant maintains that the Examiner's rejections have been overcome, and respectfully requests that they be withdrawn.

Formalities

Abstract of the Disclosure

The Examiner objected to the Abstract of the Disclosure as longer than 150 words. In response, applicant notes that a substitute abstract has been submitted as **Exhibit A**. Applicant maintains that the substitute abstract satisfies the requirements of 37 C.F.R. §1.72(b).

Brief Description of the Figures

The Examiner objected to the Brief Description of the Figures as allegedly lacking proper description for Figure 5. In response, but without conceding the correctness of the Examiner's objection, applicant notes that the specification has been amended to reflect Figure 5A and 5B, thereby obviating the Examiner's objection.

Claim Objection

The Examiner objected to claim 16 as allegedly lacking proper form. Specifically, the Examiner alleges that claim 16 improperly refers to Table 3 in identifying the relevant

genetic alterations. In response, but without conceding the correctness of the Examiner's objection, applicant notes that claim 16 has been amended to specifically recite the relevant claimed genetic alterations set forth in Table 3, thereby obviating the Examiner's objection.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 101-106 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that claim 101 as written is not enabled for expression in a host cell in a whole organism.

In response, applicant respectfully traverses the Examiner's rejection. Specifically, applicant notes that claim 101 as amended, provides a vector adapted for expression in a host cell *in vitro*, and not in a whole organism. Thus, the Examiner's rejection is obviated.

The Examiner further rejected claims 1-7, 12-16, 21-22 and 98-106 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the claims lack written description because the specification as filed does not teach that applicant was in possession of a

representative number of species of the genus of nucleic acid molecules that encode a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein.

In response, applicant respectfully traverses the Examiner's rejection.

The test for written description under 35 U.S.C. §112, first paragraph, is whether the disclosure describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. According to M.P.E.P. §2163(I)(A), when evaluating whether support in the specification for the original claims is sufficient, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). The initial burden is therefore on the Examiner to present evidence of the lack of written description. Applicant maintains that the claimed invention satisfies the test for adequate written description, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

The subject invention provides mammalian nucleic acid molecules encoding a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (EXT) protein (TREX), TREX mutants and vectors. This invention is based on applicant's discovery of a novel gene and its characterization as a TRAF-interacting EXT gene family member.

In support of the rejection, the Examiner alleges that only human TREX cDNA (SEQ ID NO:3) is disclosed in the application, and does not provide by itself a representative number of species for the claimed genus. The Examiner further alleges that the only mutant disclosed is the 9-bp insertion in the TREX DNA found in a patient with thyroid cancer which, by itself, does not provide adequate description for the claimed genus.

Applicant disagrees with the Examiner's assertions and notes that the specification discloses additional sequences and additional modifications associated with TREX. Applicant directs the Examiner's attention to the specification, *inter alia*, at page 15, line 3 to page 16, line 10, describing different embodiments of the subject invention. These include, but are not limited to, mouse TREX cDNA and protein, also described in Figures 7A-7B, Figures 9A-9B, and disclosed as SEQ ID NO:1 (Mouse TREX cDNA sequence) and SEQ ID NO:2 (Mouse TREX protein sequence). Applicant further directs the Examiner's attention to the specification, *inter alia*, at page 53, lines 7-33, detailing some of the possible genetic alterations of TREX. These are summarized in Table 3 and include a 9-bp insertion between nucleotide 758 and nucleotide 759, a base substitution of nucleotide 1106 from G to A, a base substitution of nucleotide 1820 from A to G, and a base substitution of nucleotide 2408 from C to T.

Moreover, according to M.P.E.P. §2163 (II)(A)(3)(a)(ii), the written description for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics sufficient to show the applicant was in possession of the claimed genus. *Regents of the University of California v Eli Lilly*, 119 F3d.

1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). Satisfactory disclosure depends on whether the necessary common attributes of the genus are recognized by one skilled in the art in view of the species disclosed. It does not require that the description be so specific as to fully describe all species in the genus. Applicant maintains that the claimed genus is supported by the disclosed species, and that the species disclose the necessary attributes of the claimed genus.

The claimed genus comprises mammalian nucleic acid molecules encoding a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (EXT) protein (TREX). The disclosed species include full-length cDNAs which are characterized by a TRAF-binding domain, and high homology to the EXT gene family. Applicant maintains that one skilled in the art would easily recognize these necessary common attributes of the claimed genus in view of the disclosed species.

In view of these remarks, applicant maintains that claims 1-5, 7, 12, 13, 16, 21, 22 and 98-106 are adequately supported by the disclosure and satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102(a)

The Examiner rejected claims 1-7, 12-15, 21, 22 and 101-106 under 35 U.S.C. §102(a) as allegedly anticipated by GenEmbl AF001690, Van Hul et al., Genomics 47(2), 230-237 (1998), and GenEmbl AB011091. Specifically, the Examiner alleges that the sequence as set forth in SEQ ID NO:3 in the subject

application is taught by GenEmbl AF001690, and that vectors, host cells containing these vectors and the sequence as set forth in SEQ ID NO:4 in the subject application, including the zipper motif and EXT C domain, are taught by Van Hul, et al.

In response, applicant respectfully traverses the Examiner's rejection.

Under 35 U.S.C. §102(a), a person shall be entitled to a patent unless the invention was known or used by others in this country, or patented, or described in a printed publication in this or a foreign country, before the invention thereof by applicant for a patent. Under 37 C.F.R. §1.131, when any claim of an application is rejected, the inventor of the subject matter may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference on which the rejection is based.

Applicant maintains that the subject matter of the rejected claims was invented prior to January 15, 1998, the earliest effective date of the cited references. In support of this position, applicant submits a Declaration under 37 C.F.R. §1.131, annexed hereto as **Exhibit E**.

In the Declaration, applicant Dr. Taka Aki Sato declares that he is the sole inventor of the subject matter encompassed by the claims of the above-identified application as amended herein (the "claimed invention").

Dr. Sato also declares that the claimed invention encompasses, and is exemplified by, an isolated nucleic acid encoding a

mammalian Tumor necrosis factor Receptor-Associated Factor ("TRAF") protein-interacting hereditary multiple extoses ("TREX") protein (the "claimed nucleic acid").

Dr. Sato further declares that he has read the Office Action issued on November 22, 2002 by the United States Patent and Trademark Office in connection with the subject application and understands that in the Office Action, certain claims of the subject application encompassing the claimed nucleic acid have been rejected as allegedly anticipated by GenEmbl AF001690 (dated February 20, 1998), Van Hul et al., *Genomics* 47(2), 230-237 (dated January 15, 1998), and GenEmbl AB011091 (dated April 10, 1998).

Dr. Sato declares that the claimed nucleic acid was conceived solely by him in the United States prior to January 15, 1998.

Dr. Sato also declares that in accordance with his conception of the claimed nucleic acid, experiments were conducted either directly by him, or by others under his direction and supervision, to reduce the claimed nucleic acid to practice in the United States prior to January 15, 1998.

Specifically, Dr. Sato declares that detailed in paragraphs 7-9 of the Declaration are experiments which he and/or those working under his direction and supervision performed in the United States prior to January 15, 1998 to isolate nucleic acid encoding the protein designated "CAP-2" and later renamed "TREX" protein.

Dr. Sato declares that to isolate cells comprising CAP-2-encoding nucleic acid, he and/or those working under his

direction and supervision performed a yeast two hybrid screening experiment. This experiment employed yeast L40 strain cells containing two types of plasmids. The first type of plasmid was designated "pBTM116" and contained a human TRAF-3-encoding sequence. The second type of plasmid was designated "pVP16" and contained a portion of a mouse embryo cDNA library. This screening experiment resulted in the isolation of cells comprising mouse CAP-2-encoding nucleic acid in the form of cDNA. As evidence of the performance of this screening experiment, Dr. Sato attaches to the Declaration as **Exhibit 1** a copy of pages 7-9 from the laboratory notebook of Dr. Junn Yanagisawa who, at the time of this experiment, was a post-doctoral fellow in his laboratory working under his direction and supervision. It is noted that annexed pages 7-9 in fact constitute six pages, in that there exist two separate notebook pages designated "007", two separate notebook pages designated "008" and two separate notebook pages designated "009."

Dr. Sato also declares that he and/or those working under his direction and supervision isolated cDNA encoding a portion of mouse CAP-2 ("mouse cDNA") from the cells isolated in the screening experiment described in paragraph 7 of the Declaration. Dr. Sato and/or those working under his direction and supervision then determined the sequence of the isolated mouse cDNA. As evidence of the isolation and sequencing of the mouse cDNA, Dr. Sato attaches to the Declaration as **Exhibit 2** a copy of an annotated document setting forth the nucleic acid sequence of the mouse cDNA and the amino acid sequence encoded thereby.

Finally, Dr. Sato declares that he and/or those working under his direction and supervision employed the mouse cDNA isolated in the experiment described in paragraph 8 of the Declaration to isolate a cDNA encoding a full-length human CAP-2 protein ("human cDNA"). Dr. Sato and/or those working under his direction and supervision then determined the nucleic acid sequence of the isolated human cDNA. As evidence of the isolation and sequencing of the human cDNA, Dr. Sato attaches to the Declaration as **Exhibit 3** a copy of an annotated document setting forth the nucleic acid sequence of the isolated human cDNA, as well as the amino acid sequences encoded by each of the three reading frames thereof.

Applicant maintains that the Declaration under 37 C.F.R. §1.131 establishes conception and reduction to practice of the claimed invention prior to January 15, 1998, and overcomes the rejection of claims 1-5, 7, 12, 13, 16, 21, 22 and 98-106 under 35 U.S.C. §102(a) by antedating the references cited in support thereof.

In view of these remarks, applicant maintains that claims 1-5, 7, 12, 13, 16, 21, 22 and 98-106 satisfy the requirements of 35 U.S.C. §102(a).

Summary

In view of the arguments set forth above, applicant maintains that the Examiner's rejections have been overcome. Applicant respectfully requests that the Examiner reconsider and withdraw same, and earnestly solicits allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $205.00 for the two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

4/22/03

Alan J. Morrison Date
Reg. No. 37,399

John P. White, Esq.
Registration No. 28,678
Alan J. Morrison, Esq.
Registration No. 37,399
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

Marked-up Version of the Abstract of the Disclosure

Abstract of the Disclosure

This invention provides an isolated nucleic acid molecule encoding a Tumor necrosis factor Receptor-Associated Factor [(TRAF)] protein-interacting hereditary multiple extoses (TREX) protein[.] and [This invention also provides] vectors comprising the isolated nucleic acid [molecule] encoding [a] TREX [protein]. This invention also [further] provides a purified TREX protein and antibodies thereto. This invention further provides oligonucleotides [comprising a nucleic acid molecule of at least 15 nucleotides] capable of specifically hybridizing with [a unique sequence included within] the [sequence of an] isolated nucleic acid molecule encoding TREX [protein]. This invention further provides an antisense oligonucleotide [comprising a sequence capable of specifically hybridizing with a unique sequence included within] against a genomic DNA molecule encoding [a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses [()]TREX[)] [protein]. [This invention provides a monoclonal antibody directed to an epitope of a TREX protein.] This invention further provides methods of (1) inhibiting TREX protein interaction[;], (2) inhibiting overexpression of TREX protein, and (3) [with a TRAF protein; of] inhibiting growth of a tumor[;]. [of treating abnormalities in a subject associated with overexpression of TREX.] This invention provides assays for (1) screening for compounds that inhibit TREX binding, (2) detecting predispositions to cancer comprising TREX mutations, and (3) diagnosing cancer comprising TREX mutations. Finally, [T]this invention

provides pharmaceutical compositions comprising oligonucleotides [effective to the] that prevent overexpression of [a] TREX, or antibodies [effective to block binding of a TREX, or protein to a TRAF protein binding; of detecting predispositions to cancers comprising TREX mutations; and of diagnosing cancer comprising TREX mutations] that inhibit binding of TREX.

Marked-up Version of the Specification Paragraph

Figure 5A-5B. Chromosomal mapping of the TREX gene on chromosome 8p12-p21. The biotin-labeled TREX cDNA probe and the digoxigenin-labeled chromosome 8 centromere-specific probe were cohybridized [to a normal human metaphase (a) or prophase (b) spreads] and detected [with avidin FITC (green signals) and anti-digoxigenin-rhodamine (red signals), respectively]. Chromosomes were counterstained with DAPI (blue). Fig. 5A shows the cohybridization to normal human metaphase spreads detected with avidin FITC (green signals). Fig. 5B shows the cohybridization to normal human prophase spreads detected with anti-digoxigenin-rhodamine (red signals).

Marked-up Version of the Claims

1. (Amended) An isolated nucleic acid molecule encoding a mammalian Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein.

5. (Amended) The isolated nucleic acid molecule of claim 1, wherein the nucleic acid molecule is an RNA molecule.

7. (Amended) The isolated nucleic acid molecule of claim 1, [wherein the mammalian Tumor necrosis factor Receptor-Associated Factor (TRAF)m protein-interacting hereidatry multiple extose (TREX) protein is] wherein the nucleic acid molecule encodes a mouse [,rat,] or human Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein.

12. (Amended) The isolated nucleic acid molecule of claim [6] 1, wherein the nucleic acid molecule encodes a Tumor nerosis factor Receptor-Associated Factor (TRAF)protein-interacting hereditary multiple extoses (TREX) protein comprising an amino acid sequence as set forth in [Figure 8B (]SEQ ID NO:4[)].

16. (Amended) An isolated nucleic acid molecule encoding a mutant homolog of the mammalian Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein [whose

genetic alteration is set forth in Table 3] comprising a genetic alteration selected from the group consisting of a 9-bp insertion between nucleotide 758 and nucleotide 759, a base substitution of nucleotide 1106 from G to A, a base substitution of nucleotide 1820 from A to G, and a base substitution of nucleotide 2408 from C to T.

21. (Amended) The isolated nucleic acid molecule of claim [6] 1, wherein the [mammalian TREX comprises a human] nucleic acid molecule comprises the nucleic acid sequence set forth in [Figure 8A ()]SEQ ID NO:3[)].

98. (Amended) The isolated nucleic acid molecule of claim 12, [which] wherein the nucleic acid molecule is a deletion mutant.

101. (Amended) The vector of claim 22 adapted for expression in a host cell *in vitro* which comprises the regulatory elements necessary for expression of the nucleic acid molecule in the host cell operatively linked to the nucleic acid molecule encoding the Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein, so as to permit expression of the TREX protein.

ligation

pBTM116 Eco / Bam cut CIP. 1µg.
Double stranded oligomer (1/10)
↓
EtOH

→ ligation 4°C 2days

CAP2. FAP2 cuing 開始
3ml ~~Phop~~ Ade His Leu Trp.
CAP2 colonies | 128 clones
FAP2 colonies | 112 clones
} incubation

NA culture start.

Mating strain ~~stra~~ transformation.

pBWT 116 – CAP#7
pBWT 116 – FAP } transformation in NA
pBWT 116 – lamin

~~XR~~ XLI Blue MRF' } culture start.
DH5α.

Random oligo Fas 15aa library transformation

Random oligo ligated in pBWT 116
↓ cut SnaI 1hr.

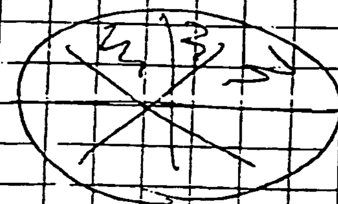
Transformation XLI Blue MRF' (stratagene.)

XLI Blue MRF' } preparation of competent cells
DH5α.

CAP2 FAP2 carrying ~~[illegible]~~ clones striking.

↓

plating Ade His Trp



CAP2 128 clones

FAP2 112 clones.

Random mutated ~~[illegible]~~ H Fas 15aa oligo – pBMT116

↓ ≃10^4 colonies/plate × 10.

≃ 10^5 colonies.

pick up 10 colonies.

↓ 3ml LB amp culture. o/n.

library check & large scale prep.

- Random Fos 15aa - pBMT116.
  - ↓ miniprep. 10 colonies.
    check.
    (Sma I site)

- large culture 400ml random Fos 15aa - pBMT116
  - → 3P. glycerol stock - 80°C
  - ↓
  - QIAGEN. MAXI prep.
    - 400μg DNA

- CAP2. FAP2 ligation.

large scale transformation in L40.

(pBAIT 116 Human Fetal brain)
library. 500 μg.

↓ Ade 20 plates. 10 ml. 500 μl/plates
check Ade His
1/100 1/1000 1/10000.
Small plates

FAP2 CAP2 colony pickups.

↳ Master plates His Ade cups 50

2·10⁷ 10⁶ 100 2 5

library transformation 20.

~~1/10000 57~~ 5.7×10⁴ 5.7×10⁵ ×20.

~~1/1000 400~~ 5.7×2 ×10⁶
1.14 | 1.14×10⁷ |

Ade His 1.14×10⁷ colonies.

His. 7. 3PB以上に多い.

↓ try again
DNA 500μg → 5μg

large scale transformation in L40

pBMTH6 - Human Mutated Fas 15aa

5 µg

↓ x20 plates (Ade)

small plates. 1/10 1/100

FAP2 CAP2 Master plates replicas Ade His Trp

↓ Ade His check

library Transformation

~~100~~ → 117 colonies

$117 \times 100 \times 200 \rightarrow 2.3 \times 10^5$

colonies

FAST growth 232 colonies

Medium 321

Slow. 339

Total 892 colonies.

Results

2.3×10^5 colonies

↓

892

Colony pick up

DNA Strider™ 1.2 ## [redacted] 3:31:10 P[redacted]

128 Full -> 1-phase Translation

DNA sequence 426 b.p. AGCCCTCGGGCT ... tttgcctttgat linear

```
1/1                                     31/11
AGC CCT CGG GCT GGC AGT GAG CTC TGT GAG GTA AAG CAT GTc CTT GAC CCC TGT CGG ATT
ser pro arg ala gly ser glu (leu) cys glu val lys his val (leu) asp pro cys arg (ile)
61/21                                   91/31
CGT GAG TCT GTG AGC GAA GAG CTT CTA CAG CTC GAA GCC AAG CGG CAG GAG CTG AAC AGC
arg glu ser val ser glu glu (leu) (leu) gln (leu) glu ala lys arg gln glu (leu) asn ser
121/41                                  151/51
GAG ATT GCC AAG CTG AAC CTC AAG ATT GAA GCC TgT aAG AAG AGC AtA GAG aAT gcc aAG
glu (ile) ala lys (leu) asn (leu) lys (ile) glu ala cys lys lys ser (ile) glu asn ala lys
181/61                                  211/71
cAg GAC CTg Ctg cag ctc aag aat gtc att agc cag aca gag cac tcc tac aag gag ctg
gln asp (leu) (leu) gln (leu) lys asn val (ile) ser gln thr glu his ser tyr lys glu (leu)
241/81                                  271/91
atg gcc cag aac cag ccc aaa ctg tcc ctg ccc atc cga ctg ctc cct gag aag gac gat
met ala gln asn gln pro lys (leu) ser (leu) pro (ile) arg (leu) (leu) pro glu lys asp asp
301/101                                 331/111
gcc ggc ctt cca ccc ccc aag gtc act cgg ggt tgc cgc ctt cac aac tgc ctt gat tac
ala gly (leu) pro pro pro lys val thr arg gly cys arg (leu) his asn cys (leu) asp tyr
361/121                                 391/131
tct cgt tgt cct ctg acg tct ggc ttt ccc gtc tac gtc tat gac agt gac cag ttt gcc
ser arg cys pro (leu) thr ser gly phe pro val tyr val tyr asp ser asp gln phe ala
421/141
ttt gat
phe asp
```

(L) - 7 - (IL) - 4 - (L) - 8 - L - 9 - L

(ile) - 7 - (ile) - 7 - (ile) - 7 - (Leu 7 ile)

DNA Strider™ 1.2 ## 7 7 PM

CAP-2FULL.9/4 -> 3-phase Translation hcap-2. cDNA

DNA sequence 2761 b.p. atgacaggctat ... AAGTTCATCTAG linear

```
1/1                                                31/11
atg aca ggc tat acc atg ctg cgg aat ggg ggc gcg ggg aac gga ggt cag acc tgc atg
M   T   G   Y   T   M   L   R   N   G   G   A   G   N   G   G   Q   T   C   M
  *   Q   A   I   P   C   C   G   M   G   A   R   G   T   E   V   R   P   A   C
    D   R   L   Y   H   A   A   E   W   G   R   G   E   R   R   S   D   L   H   A
61/21                                              91/31
ctg cgc tgg tcc aac cgc atc cgc ctc acg tgg ctc agc ttc acg ctc ttt gtc atc ctg
L   R   W   S   N   R   I   R   L   T   W   L   S   F   T   L   F   V   I   L
  C   A   G   P   T   A   S   A   S   R   G   S   A   S   R   S   L   S   S   W
    A   L   V   Q   P   H   P   P   H   V   A   Q   L   H   A   L   C   H   P   G
121/41                                             151/51
gtc ttc ttc ccg ctc atc gcc cac tat tac ctc acc act ctg gat gag gct gat gag gca
V   F   F   P   L   I   A   H   Y   Y   L   T   T   L   D   E   A   D   E   A
  S   S   S   R   S   S   P   T   I   T   S   P   L   W   M   R   L   M   R   Q
    L   L   P   A   H   R   P   L   L   P   H   H   S   G   *   G   *   *   G   R
181/61                                             211/71
ggc aag cgg att ttt ggt ccc cgg gtg ggg aac gag ctg tgc gag gtg aag cac gtg ctg
G   K   R   I   F   G   P   R   V   G   N   E   L   C   E   V   K   H   V   L
  A   S   G   F   L   V   P   G   W   G   T   S   C   A   R   *   S   T   C   W
    Q   A   D   F   W   S   P   G   G   E   R   A   V   R   G   E   A   R   A   G
241/81                                             271/91
gat ctg tgc cgc atc cgg gag tcg gtg agt gaa gag ctc ctg cag ctg gag gcc aag cgc
D   L   C   R   I   R   E   S   V   S   E   E   L   L   Q   L   E   A   K   R
  I   C   A   A   S   G   S   R   *   V   K   S   S   C   S   W   R   P   S   A
    S   V   P   H   P   G   V   G   E   *   R   A   P   A   A   G   G   Q   A   P
301/101                                            331/111
caa gag ctg aac agc gag atc gcc aag ctg aat ctg aag atc gaa gcc tgt aag aag agc
Q   E   L   N   S   E   I   A   K   L   N   L   K   I   E   A   C   K   K   S
  K   S   *   T   A   R   S   P   S   *   I   *   R   S   K   P   V   R   R   A
    R   A   E   Q   R   D   R   Q   A   E   S   E   D   R   S   L   *   E   E   H
361/121                                            391/131
att gag aac gcc aag cag gac ctg ctc cag ctc aag aat gtc atc agc cag acc gag cat
I   E   N   A   K   Q   D   L   L   Q   L   K   N   V   I   S   Q   T   E   H
  L   R   T   P   S   R   T   C   S   S   S   R   M   S   S   A   R   P   S   I
    *   E   R   Q   A   G   P   A   P   A   Q   E   C   H   Q   P   D   R   A   F
421/141                                            451/151
tcc tac aag gag ctc atg gcc cag aac cag ccc aag ctg tcc ctg ccc atc cga ctg ctc
S   Y   K   E   L   M   A   Q   N   Q   P   K   L   S   L   P   I   R   L   L
  P   T   R   S   S   W   P   R   T   S   P   S   C   P   C   P   S   D   C   S
    L   Q   G   A   H   G   P   E   P   A   Q   A   V   P   A   H   P   T   A   P
481/161                                            511/171
cca gag aag gac gat gcc ggc ctc cct ccc ccg aag gcc act cgg ggc tgc cgg cta cac
P   E   K   D   D   A   G   L   P   P   P   K   A   T   R   G   C   R   L   H
  Q   R   R   T   M   P   A   S   L   P   R   R   P   L   G   A   A   G   Y   T
    R   E   G   R   C   R   P   P   S   P   E   G   H   S   G   L   P   A   T   Q
541/181                                            571/191
aac tgc ttt gat tat tct cgt tgc cct ctc acc tct ggc ttc ccg gtc tac gtc tat gac
N   C   F   D   Y   S   R   C   P   L   T   S   G   F   P   V   Y   V   Y   D
  T   A   L   I   I   L   V   A   L   S   P   L   A   S   R   S   T   S   M   T
    L   L   *   L   F   S   L   P   S   H   L   W   L   P   G   L   R   L   *   Q
601/201                                            631/211
agt gac cag ttt gtc ttt ggc agc tac ctg gat ccc ttg gtc aag cag gct ttt cag gcg
S   D   Q   F   V   F   G   S   Y   L   D   P   L   V   K   Q   A   F   Q   A
  V   T   S   L   S   L   A   A   T   W   I   P   W   S   S   R   L   F   R   R
    *   P   V   C   L   W   Q   L   P   G   S   L   G   Q   A   G   F   S   G   D
661/221                                            691/231
aca gca cga gct aac gtt tat gtt aca gaa aat gca gac atc gcc tgc ctt tac gtg ata
T   A   R   A   N   V   Y   V   T   E   N   A   D   I   A   C   L   Y   V   I
  Q   H   E   L   T   F   M   L   Q   K   M   Q   T   S   P   A   F   T   *   Y
    S   T   S   *   R   L   C   Y   R   K   C   R   H   R   L   P   L   R   D   T
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721/241                                                                751/251
cta gtg gga gag atg cag gag ccg gtg gtg ctg cgg cct gct gag ctg gag aag cag ttg
L  V  G  E  M  Q  E  P  V  V  L  R  P  A  E  L  E  K  Q  L
 *  W  E  R  C  R  S  R  W  C  C  G  L  L  S  W  R  S  S  C
  S  G  R  D  A  G  A  G  G  A  A  A  C  *  A  G  E  A  V  V
781/261                                                                811/271
tat tcc ctg cca cac tgg cgg acg gat gga cac aac cat gtc atc atc aat ctg tca cgt
Y  S  L  P  H  W  R  T  D  G  H  N  H  V  I  I  N  L  S  R
 I  P  C  H  T  G  G  R  M  D  T  T  M  S  S  S  I  C  H  V
  F  P  A  T  L  A  D  G  W  T  Q  P  C  H  H  Q  S  V  T  *
841/281                                                                871/291
aag tca gat aca cag aac ctt ctc tat aac gtc agt act ggc cgt gcc atg gtg gcc cag
K  S  D  T  Q  N  L  L  Y  N  V  S  T  G  R  A  M  V  A  Q
 S  Q  I  H  R  T  F  S  I  T  S  V  L  A  V  P  W  W  P  S
  V  R  Y  T  E  P  S  L  *  R  Q  Y  W  P  C  H  G  G  P  V
901/301                                                                931/311
tcc acc ttc tac act gtc cag tac aga cct ggc ttt gac ttg gtc gta tca ccg ctg gtc
S  T  F  Y  T  V  Q  Y  R  P  G  F  D  L  V  V  S  P  L  V
 P  P  S  T  L  S  S  T  D  L  A  L  T  W  S  Y  H  R  W  S
  H  L  L  H  C  P  V  Q  T  W  L  *  L  G  R  I  T  A  G  P
961/321                                                                991/331
cat gcc atg tct gag ccc aac ttc atg gaa atc cca cca cag gtg ccg gtg aag cgg aaa
H  A  M  S  E  P  N  F  M  E  I  P  P  Q  V  P  V  K  R  K
 M  P  C  L  S  P  T  S  W  K  S  H  H  R  C  R  *  S  G  N
  C  H  V  *  A  Q  L  H  G  N  P  T  T  G  A  G  E  A  E  I
1021/341                                                               1051/351
tat ctc ttc acc ttc cag ggc gag aag att gag tct ctg agg tct agc ctt cag gag gcc
Y  L  F  T  F  Q  G  E  K  I  E  S  L  R  S  S  L  Q  E  A
 I  S  S  P  S  R  A  R  R  L  S  L  *  G  L  A  F  R  R  P
  S  L  H  L  P  G  R  E  D  *  V  S  E  V  *  P  S  G  G  P
1081/361                                                               1111/371
cgc tcc ttc gaa gag gaa atg gag ggc gac cct ccc gcc gac tac gat gac cgg atc att
R  S  F  E  E  E  M  E  G  D  P  P  A  D  Y  D  D  R  I  I
 A  P  S  K  R  K  W  R  A  T  L  P  P  T  T  M  T  G  S  L
  L  L  R  R  G  N  G  G  R  P  S  R  R  L  R  *  P  D  H  C
1141/381                                                               1171/391
gcc acc ctg aag gcg gtg cag gac agc aag ctg gat cag gtc ctg gtg gaa ttc ACC TGC
A  T  L  K  A  V  Q  D  S  K  L  D  Q  V  L  V  E  F  T  C
 P  P  *  R  R  C  R  T  A  S  W  I  R  S  W  W  N  S  P  A
  H  P  E  G  G  A  G  Q  Q  A  G  S  G  P  G  G  I  H  L  Q
1201/401                                                               1231/411
AAA AAC CAG CCC AAA CCC AGC CTG CCG ACT GAG TGG GCA CTG TGT GGA GAG CGG GAG GAC
K  N  Q  P  K  P  S  L  P  T  E  W  A  L  C  G  E  R  E  D
 K  T  S  P  N  P  A  C  Q  L  S  G  H  C  V  E  S  G  R  T
  K  P  A  Q  T  Q  P  A  N  *  V  G  T  V  W  R  A  G  G  P
1261/421                                                               1291/431
CGC TTG GAA TTG CTG AAG GCT CTC CAC CTT CGC CCT CAT CAT TAC CCC CGG GGA CCC TCG
R  L  E  L  L  K  A  L  H  L  R  P  H  H  Y  P  R  G  P  S
 A  W  N  C  *  R  L  S  T  F  A  L  I  I  T  P  G  D  P  R
  L  G  I  A  E  G  S  P  P  S  P  S  S  L  P  P  G  T  L  A
1321/441                                                               1351/451
CTT GGT TAT TTC CTC TGG GTG TGC AAC ACG GCT CTT CGA AGC CCT GGA AGT CGG TGC CGT
L  G  Y  F  L  W  V  C  N  T  A  L  R  S  P  G  S  R  C  R
 L  V  I  S  S  G  C  A  T  R  L  F  E  A  L  E  V  G  A  V
  W  L  F  P  L  G  V  Q  H  G  S  S  K  P  W  K  S  V  P  S
1381/461                                                               1411/471
CCC GGT GGT GCT GGG GGA GCA GGT CCA GCT TCC CTA CCA GGA CAT GCT GCA GTG GAA CGA
P  G  G  A  G  G  A  G  P  A  S  L  P  G  H  A  A  V  E  R
 P  V  V  L  G  E  Q  V  Q  L  P  Y  Q  D  M  L  Q  W  N  E
  R  W  C  W  G  S  R  S  S  F  P  T  R  T  C  C  S  G  T  R
1441/481                                                               1471/491
GGC GGC CCT GGT GGT GCC AAA GCC TCG TGT TAC CGA GGT TCA TTT CCT GCT CAG AAG CCT
G  G  P  G  G  A  K  A  S  C  Y  R  G  S  F  P  A  Q  K  P
 A  A  L  V  V  P  K  P  R  V  T  E  V  H  F  L  L  R  S  L
  R  P  W  W  C  Q  S  L  V  L  P  R  F  I  S  C  S  E  A  S
1501/501                                                               1531/511
CTC CGA TAG TGA CCT CCT GGC TAT GAG GCG GCA AGG CCG CTT TCT CTG GGA GAC TTA CTT
L  R  *  *  P  P  G  Y  E  A  A  R  P  L  S  L  G  D  L  L
 S  D  S  D  L  L  A  M  R  R  Q  G  R  F  L  W  E  T  Y  F
  P  I  V  T  S  W  L  *  G  G  K  A  A  F  S  G  R  L  T  S
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1561/521                                                    1591/531
CCC CAC TGC TGA CAG TAT TTT TAA TAC CGT GCT GGC TAT GAT TAG GAC TCG CAT CCA GAT
P   H   C   *   Q   Y   F   *   Y   R   A   G   Y   D   *   D   S   H   P   D
 P   T   A   D   S   I   F   N   T   V   L   A   M   I   R   T   R   I   Q   I
  P   L   L   T   V   F   L   I   P   C   W   L   *   L   G   L   A   S   R   S
1621/541                                                    1651/551
CCC AGC CGC TCC CAT CCG GGA AGA GGC GGC AGC TGA GAT CCC CCA CCG TTC AGG CAA GGC
P   S   R   S   H   P   G   R   G   G   S   *   D   P   P   P   F   R   Q   G
 P   A   A   P   I   R   E   E   A   A   A   E   I   P   H   R   S   G   K   A
  Q   P   L   P   S   G   K   R   R   Q   L   R   S   P   T   V   Q   A   R   R
1681/561                                                    1711/571
GGC TGG AAC TGA CCC CAA CAT GGC TGA CAA CGG GGA CCT GGA CCT GGG GCC AGT GGA GAC
G   W   N   *   P   Q   H   G   *   Q   R   G   P   G   P   G   A   S   G   D
 A   G   T   D   P   N   M   A   D   N   G   D   L   D   L   G   P   V   E   T
  L   E   L   T   P   T   W   L   T   T   G   T   W   T   W   G   Q   W   R   R
1741/581                                                    1771/591
GGA GCC GCC CTA CGC CTC ACC CAG ATA CCT CCG CAA TTT CAC TCT GAC TGT CAC TGA CTT
G   A   A   L   R   L   T   Q   I   P   P   Q   F   H   S   D   C   H   *   L
 E   P   P   Y   A   S   P   R   Y   L   R   N   F   T   L   T   V   T   D   F
  S   R   P   T   P   H   P   D   T   S   A   I   S   L   *   L   S   L   T   F
1801/601                                                    1831/611
TTA CCG CAG CTG GAA CTG TGC TCC AGG GCC TTT CCA TCT TTT CCC CCA CAC TCC CTT TGA
L   P   Q   L   E   L   C   S   R   A   F   P   S   F   P   P   H   S   L   *
 Y   R   S   W   N   C   A   P   G   P   F   H   L   F   P   H   T   P   F   D
  T   A   A   G   T   V   L   Q   G   L   S   I   F   S   P   T   L   P   L   T
1861/621                                                    1891/631
CCC TGT GTT GCC CTC AGA GGC CAA ATT CTT GGG CTC AGG GAC TGG CTT TCG GCC TAT TGG
P   C   V   A   L   R   G   Q   I   L   G   L   R   D   W   L   S   A   Y   W
 P   V   L   P   S   E   A   K   F   L   G   S   G   T   G   F   R   P   I   G
  L   C   C   P   Q   R   P   N   S   W   A   Q   G   L   A   F   G   L   L   V
1921/641                                                    1951/651
TGG TGG AGC TGG GGG TTC TGG CAA GGA ATT TCA GGC AGC GCT TGG AGG CAA TGT TCC CCG
W   W   S   W   G   F   W   Q   G   I   S   G   S   A   W   R   Q   C   S   P
 G   G   A   G   G   S   G   K   E   F   Q   A   A   L   G   G   N   V   P   R
  V   E   L   G   V   L   A   R   N   F   R   Q   R   L   E   A   M   F   P   E
1981/661                                                    2011/671
AGA GCA GTT CAC GGT GGT GAT GTT GAC TTA TGA GCG GGA GGA AGT GCT TAT GAA CTC TTT
R   A   V   H   G   G   D   V   D   L   *   A   G   G   S   A   Y   E   L   F
 E   Q   F   T   V   V   M   L   T   Y   E   R   E   E   V   L   M   N   S   L
  S   S   S   R   W   *   C   *   L   M   S   G   R   K   C   L   *   T   L   *
2041/681                                                    2071/691
AGA GAG GCT GAA TGG CCT CCC TTA CCT GAA CAA GGT CGT GGT GGT GTG GAA TTC TCC CAA
R   E   A   E   W   P   P   L   P   E   Q   G   R   G   G   V   E   F   S   Q
 E   R   L   N   G   L   P   Y   L   N   K   V   V   V   V   W   N   S   P   K
  R   G   *   M   A   S   L   T   *   T   R   S   W   W   C   G   I   L   P   S
2101/701                                                    2131/711
GCT GCC ATC AGA GGA CCT TCT GTG GCC TGA CAT TGG CGT CCC CAT CAT GGT GGT CCG TAC
A   A   I   R   G   P   S   V   A   *   H   W   R   P   H   H   G   G   P   Y
 L   P   S   E   D   L   L   W   P   D   I   G   V   P   I   M   V   V   R   T
  C   H   Q   R   T   F   C   G   L   T   L   A   S   P   S   W   W   S   V   L
2161/721                                                    2191/731
TGA GAA GAA CAG TTT GAA CAA CCG ATT CTT ACC CTG GAA TGA AAT TGA GAC AGA GGC CAT
*   E   E   Q   F   E   Q   P   I   L   T   L   E   *   N   *   D   R   G   H
 E   K   N   S   L   N   N   R   F   L   P   W   N   E   I   E   T   E   A   I
  R   R   T   V   *   T   T   D   S   Y   P   G   M   K   L   R   Q   R   P   S
2221/741                                                    2251/751
CCT GTC CAT TGA TGA CGA TGC TCA CCT CCG CCA TGA CGA AAT CAT GTT TGG GTT CCG GGT
P   V   H   *   *   R   C   S   P   P   P   *   R   N   H   V   W   V   P   G
 L   S   I   D   D   D   A   H   L   R   H   D   E   I   M   F   G   F   R   V
  C   P   L   M   T   M   L   T   S   A   M   T   K   S   C   L   G   S   G   C
2281/761                                                    2311/771
GTG GAG AGA AGC TCG GGA CCG CAT CGT GGG CTT CCC TGG CCG TTA CCA CGC ATG GGA CAT
V   E   R   S   S   G   P   H   R   G   L   P   W   P   L   P   R   M   G   H
 W   R   E   A   R   D   R   I   V   G   F   P   G   R   Y   H   A   W   D   I
  G   E   K   L   G   T   A   S   W   A   S   L   A   V   T   T   H   G   T   S
2341/781                                                    2371/791
CCC CCA TCA GTC CTG GCT CTA CAA CTC CAA CTA CTC CTG TGA GCT GTC CAT GGT GCT GAC
P   P   S   V   L   A   L   Q   L   Q   L   L   L   *   A   V   H   G   A   D
 P   H   Q   S   W   L   Y   N   S   N   Y   S   C   E   L   S   M   V   L   T
  P   I   S   P   G   S   T   T   P   T   T   P   V   S   C   P   W   C   *   Q
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2401/801                                                2431/811
AGG TGC TGC CTT CTT TCA CAA GTA TTA TGC CTA CCT GTA TTC TTA TGT GAT GCC CCA GGC
R   C   C   L   L   S   Q   V   L   C   L   P   V   F   L   C   D   A   P   G
 G   A   A   F   F   H   K   Y   Y   A   Y   L   Y   S   Y   V   M   P   Q   A
  V   L   P   S   F   T   S   I   M   P   T   C   I   L   M   *   C   P   R   P
2461/821                                                2491/831
CAT CCG GGA CAT GGT GGA TGA ATA CAT CAA CTG TGA GGA CAT TGC CAT GAA CTT CCT TGT
H   P   G   H   G   G   *   I   H   Q   L   *   G   H   C   H   E   L   P   C
 I   R   D   M   V   D   E   Y   I   N   C   E   D   I   A   M   N   F   L   V
  S   G   T   W   W   M   N   T   S   T   V   R   T   L   P   *   T   S   L   S
2521/841                                                2551/851
CTC CCA CAT CAC TCG GAA GCC CCC CAT CAA GGT GAC CTC ACG GTG GAC ATT CCG ATG CCC
L   P   H   H   S   E   A   P   H   Q   G   D   L   T   V   D   I   P   M   P
 S   H   I   T   R   K   P   P   I   K   V   T   S   R   W   T   F   R   C   P
  P   T   S   L   G   S   P   P   S   R   *   P   H   G   G   H   S   D   A   Q
2581/861                                                2611/871
AGG ATG CCC TCA GGC CCT GTC TCA TGA TGA CTC CCA CTT CCA CGA GCG GCA CAA GTG CAT
R   M   P   S   G   P   V   S   *   *   L   P   L   P   R   A   A   Q   V   H
 G   C   P   Q   A   L   S   H   D   D   S   H   F   H   E   R   H   K   C   I
  D   A   L   R   P   C   L   M   M   T   P   T   S   T   S   G   T   S   A   S
2641/881                                                2671/891
CAA CTT CTT CGT GAA GGT GTA CGG CTA CAT GCC CCT CCT GTA CAC GCA GTT CAG GGT GGA
Q   L   L   R   E   G   V   R   L   H   A   P   P   V   H   A   V   Q   G   G
 N   F   F   V   K   V   Y   G   Y   M   P   L   L   Y   T   Q   F   R   V   D
  T   S   S   *   R   C   T   A   T   C   P   S   C   T   R   S   S   G   W   I
2701/901                                                2731/911
TTC TGT GCT CTT CAA GAC ACG CCT GCC CCA TGA CAA GAC CAA GTG CTT CAA GTT CAT CTA
F   C   A   L   Q   D   T   P   A   P   *   Q   D   Q   V   L   Q   V   H   L
 S   V   L   F   K   T   R   L   P   H   D   K   T   K   C   F   K   F   I   *
  L   C   S   S   R   H   A   C   P   M   T   R   P   S   A   S   S   S   S
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